

Please amend page 20, line 1 as follows:

**Claims What is claimed is:**

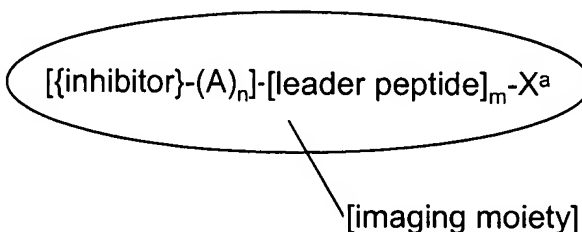
This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) An imaging agent which comprises a synthetic caspase-3 inhibitor labelled with an imaging moiety, wherein the caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than 2000 nM, and wherein following administration of said labelled caspase-3 inhibitor to the mammalian body *in vivo*, the imaging moiety can be detected either externally in a non-invasive manner or *via* use of detectors designed for use *in vivo*
2. (Cancel) The imaging agent of Claim 1, where the synthetic caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than 500 nM.
3. (Currently amended) The imaging agent of ~~Claims 1 or 2~~Claim 1, where the synthetic caspase-3 inhibitor has a molecular weight of 150 to 3000 Daltons.
4. (Currently amended) The imaging agent of ~~Claims 1 to 3~~Claim 1, where the imaging moiety comprises:
  - (i) a radioactive metal ion;
  - (ii) a paramagnetic metal ion;
  - (iii) a gamma-emitting radioactive halogen;
  - (iv) a positron-emitting radioactive non-metal;
  - (v) a hyperpolarised NMR-active nucleus;
  - (vi) an optical dye suitable for *in vivo* imaging.
5. (Currently amended) The imaging agent of ~~claims 1 to 4~~Claim 1, which further comprises a 4 to 20-mer leader peptide sequence, wherein said leader peptide

facilitates cell membrane transport from the outside to the inside of a mammalian cell *in vivo*.

6. (Currently amended) The imaging agent of Claim 5 where the synthetic caspase-3 inhibitor conjugate is of Formula I:



(Formula I)

where:

{inhibitor} is ~~the~~ a caspase-3 inhibitor with a  $K_i$  for caspase-3 of less than 2000 nM of claims 1 to 3;

[leader peptide] is as defined in Claim [4] 5 and is attached by either its' amine or carboxyl terminus;

-(A)<sub>n</sub>- is a linker group wherein each A is independently -CR<sub>2</sub>-, -CR=CR-, -C≡C-, -CR<sub>2</sub>CO<sub>2</sub>-, -CO<sub>2</sub>CR<sub>2</sub>-, -NRCO-, -CONR-, -NR(C=O)NR-, -NR(C=S)NR-, -SO<sub>2</sub>NR-, -NRSO<sub>2</sub>-, -CR<sub>2</sub>OCR<sub>2</sub>-, -CR<sub>2</sub>SCR<sub>2</sub>-, -CR<sub>2</sub>NRCR<sub>2</sub>-, a C<sub>4-8</sub> cycloheteroalkylene group, a C<sub>4-8</sub> cycloalkylene group, a C<sub>5-12</sub> arylene group, or a C<sub>3-12</sub> heteroarylene group, an amino acid or a monodisperse polyethyleneglycol (PEG) building block;

R is independently chosen from H, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> alkoxyalkyl or C<sub>1-4</sub> hydroxyalkyl;

n is an integer of value 0 to 10,

m is 0 or 1;

and X<sup>a</sup> is H, OH, Hal, NH<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxyalkyl, C<sub>1-4</sub> hydroxyalkyl or X<sup>a</sup> is the imaging moiety.

7. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the radioactive metal ion is a gamma emitter or a positron emitter.

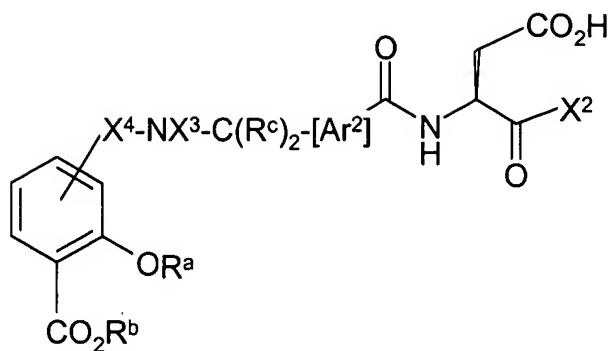
8. (Original) The imaging agent of Claim 7, where the radioactive metal ion is  $^{99m}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$  or  $^{68}\text{Ga}$ .
9. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the paramagnetic metal ion is Gd(III), Mn(II) or Fe(III).
10. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the gamma-emitting radioactive halogen is  $^{123}\text{I}$ .
11. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the positron-emitting radioactive non-metal is chosen from  $^{18}\text{F}$ ,  $^{11}\text{C}$ ,  $^{124}\text{I}$  or  $^{13}\text{N}$ .
12. (Currently amended) The imaging agent of ~~Claims 1 to 11~~Claim 1, where the synthetic caspase-3 inhibitor comprises one or more of the caspase-3 inhibitors defined in (i) to (ix):
  - (i) a tetrapeptide derivative of Formula III
 
$$\text{Z}^1\text{-Asp-Xaa1-Xaa2-Asp-X}^1 \quad (\text{III})$$
 where  $\text{Z}^1$  is a metabolism inhibiting group attached to the N-terminus of the tetrapeptide;
 

Xaa1 and Xaa2 are independently any amino acid;

$\text{X}^1$  is an  $-\text{R}^1$  or  $-\text{CH}_2\text{OR}^2$  group attached to the carboxy terminus of the tetrapeptide;

where  $\text{R}^1$  is H,  $-\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{Cl}$ ,  $\text{C}_{1-5}$  alkyl,  $\text{C}_{1-5}$  alkoxy or  $-(\text{CH}_2)_q\text{Ar}^1$ , where q is an integer of value 1 to 6 and  $\text{Ar}^1$  is  $\text{C}_{6-12}$  aryl,  $\text{C}_{5-12}$  alkyl-aryl,  $\text{C}_{5-12}$  fluoro-substituted aryl, or  $\text{C}_{3-12}$  heteroaryl;

$\text{R}^2$  is  $\text{C}_{1-5}$  alkyl,  $\text{C}_{1-10}$  acyl or  $\text{Ar}^1$ ;
  - (ii) a quinazoline or anilinoquinazoline;
  - (iii) a 2-oxindole sulphonamide;
  - (iv) an oxoazepinoindoline;
  - (v) a compound of Formula IV



(IV)

where  $\text{X}^2$  is H,  $\text{C}_{1-5}$  alkyl or  $\text{-(CH}_2)_r\text{-(S)}_s\text{-(CH}_2)_t\text{Ar}^3$ , where r and t are integers of value 0 to 6, s is 0 or 1 and  $\text{Ar}^3$  is  $\text{C}_{6-12}$  aryl,  $\text{C}_{5-12}$  alkyl-substituted aryl,  $\text{C}_{5-12}$  halo-substituted aryl, or  $\text{C}_{3-12}$  heteroaryl;

$\text{Ar}^2$  is  $\text{C}_{6-12}$  aryl or  $\text{C}_{3-12}$  heteroaryl;

$\text{X}^3$  is an  $\text{R}^b$  group;

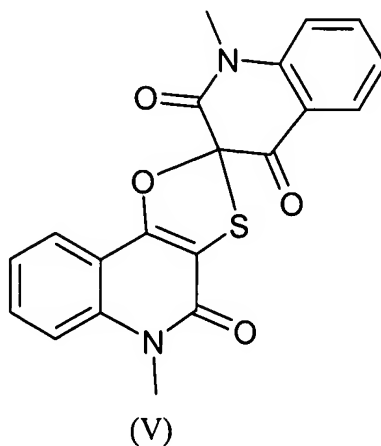
$\text{X}^4$  is  $\text{-SO}_2\text{-}$  or  $\text{-CR}_2\text{-}$

$\text{R}^a$  is H,  $\text{C}_{1-5}$  alkyl or  $\text{P}^{\text{GP}}$  where  $\text{P}^{\text{GP}}$  is a protecting group;

$\text{R}^b$  is an  $\text{R}^a$  group or  $\text{C}_{1-5}$  acyl;

each  $\text{R}^c$  is independently H or  $\text{C}_{1-5}$  alkyl;

(vi) a compound of Formula V



(V)

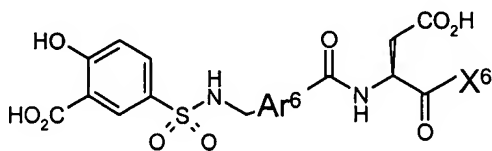
(vii) a pyrazinone;

(viii) a dipeptide of Formula VI:



where the  $\text{-CH}_2\text{SR}^1$  group is attached to the carboxy terminus of the dipeptides, and  $Z^1$  and  $R^1$  are as defined for Formula (III);

(ix) a salicylic acid sulphonamide of Formula XI:

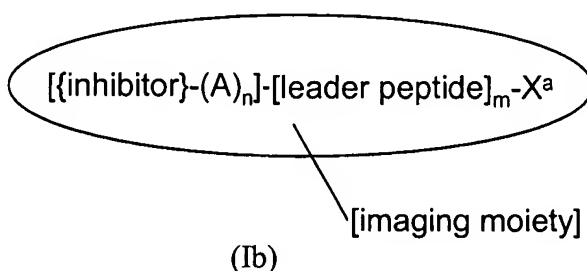


Formula XI

Where  $\text{Ar}^6$  is a 5 or 6-membered  $\text{C}_{4-6}$  aryl or heteroaryl ring, and  $\text{X}_6$  is H or  $\text{-CH}_2\text{SR}^2$ , where  $\text{R}^2$  is as defined above.

13. (Original) The imaging agent of Claim 12, where the synthetic caspase-3 inhibitor comprises:
- (i) a tetrapeptide of Formula III; or
  - (ii) a 2-oxindole sulphonamide; or
  - (iii) a dipeptide of Formula VI.
14. (Currently amended) The imaging agent of ~~Claims 1 to 13~~ Claim 1, where the synthetic caspase-3 inhibitor is selective for caspase-3 over caspase-1, by a factor of at least 50.
15. (Currently amended) The imaging agent of ~~Claims 13 or 14~~ Claim 13, where the synthetic caspase-3 inhibitor comprises a tetrapeptide of Formula III or a dipeptide of Formula VI.
16. (Currently amended) A pharmaceutical composition which comprises the imaging agent of ~~claims 1 to 15~~ Claim 1 together with a biocompatible carrier, in a form suitable for mammalian administration.

17. (Currently amended) A radiopharmaceutical composition which comprises the imaging agent of ~~claims 1 to 15~~ Claim 1 wherein the imaging moiety is radioactive, together with a biocompatible carrier, in a form suitable for mammalian administration.
18. (Original) The radiopharmaceutical composition of claim 17, where the imaging moiety comprises a positron-emitting radioactive non-metal or a gamma-emitting radioactive halogen.
19. (Original) The radiopharmaceutical composition of claim 17, where the imaging moiety comprises a radioactive metal ion.
20. (Currently amended) A conjugate of a synthetic caspase-3 inhibitor with a ligand, wherein the caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than ~~2000~~ 500 nM, and wherein said ligand is capable of forming a metal complex with a radioactive or paramagnetic metal ion.
21. (Currently amended) The conjugate of Claim 20, of Formula Ib:



where ~~A, n, m and X<sup>a</sup> are as defined in Claim 6~~

-(A)<sub>n</sub>- is a linker group wherein each A is independently -CR<sub>2</sub>-, -CR=CR-, -C≡C-, -CR<sub>2</sub>CO<sub>2</sub>-, -CO<sub>2</sub>CR<sub>2</sub>-, -NRCO-, -CONR-, -NR(C=O)NR-, -NR(C=S)NR-, -SO<sub>2</sub>NR-, -NRSO<sub>2</sub>-, -CR<sub>2</sub>OCR<sub>2</sub>-, -CR<sub>2</sub>SCR<sub>2</sub>-, -CR<sub>2</sub>NRCR<sub>2</sub>-, a C<sub>4-8</sub> cycloheteroalkylene group, a C<sub>4-8</sub> cycloalkylene group, a C<sub>5-12</sub> arylene group,

or a C<sub>3-12</sub> heteroarylene group, an amino acid or a monodisperse polyethyleneglycol (PEG) building block;

R is independently chosen from H, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> alkoxyalkyl or C<sub>1-4</sub> hydroxyalkyl;

n is an integer of value 0 to 10,

m is 0 or 1;

and X<sup>a</sup> is H, OH, Hal, NH<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxyalkyl, C<sub>1-4</sub> hydroxyalkyl or X<sup>a</sup> is the imaging moiety.

22. (Currently amended) The conjugate of ~~Claims 20 or 21~~Claim 20, wherein the ligand is a chelating agent.
23. (Original) The conjugate of Claim 22, wherein the chelating agent has a diaminedioxime, N<sub>2</sub>S<sub>2</sub>, or N<sub>3</sub>S donor set.
24. (Currently amended) A kit for the preparation of the radiopharmaceutical composition of Claim 19, which comprises the conjugate of a synthetic caspase-3 inhibitor with a ligand, wherein the caspase-3 inhibitor has a K<sub>i</sub> for caspase-3 of less than 500 nM, and wherein said ligand is capable of forming a metal complex with a radioactive or paramagnetic metal ion.~~Claims 20 to 23.~~
25. (Original) The kit of Claim 24, where the radioactive metal ion is <sup>99m</sup>Tc, and the kit further comprises a biocompatible reductant.
26. (Currently amended) A kit for the preparation of the radiopharmaceutical composition of Claim 18, which comprises a precursor, said precursor being a non-radioactive derivative of ~~the~~ a caspase-3 inhibitor of claims 1 to 15, wherein the caspase-3 inhibitor has a K<sub>i</sub> for caspase-3 of less than 2000 nM, wherein said non-radioactive derivative is capable of reaction with a source of the positron-emitting radioactive non-metal or gamma-emitting radioactive halogen to give the desired radiopharmaceutical.

27. (Original) The kit of claim 26 where the precursor is in sterile, apyrogenic form.
28. (Currently amended) The kit of ~~Claims 26 or 27~~Claim 26, where the source of the positron-emitting radioactive non-metal or gamma-emitting radioactive halogen is chosen from:
- (i) a halide ion or  $F^+$  or  $I^+$ ; or
  - (ii) b an alkylating agent chosen from an alkyl or fluoroalkyl halide, tosylate, triflate or mesylate;
29. (Currently amended) The kit of ~~Claims 26 to 28~~Claim 26, where the non-radioactive derivative is chosen from:
- (i) a an organometallic derivative such as a trialkylstannane or a trialkylsilane;
  - (ii) b a derivative containing an alkyl halide, alkyl tosylate or alkyl mesylate for nucleophilic substitution;
  - (iii) c a derivative containing an aromatic ring activated towards nucleophilic or electrophilic substitution;
  - (iv) d a derivative containing a functional group which undergoes facile alkylation;
  - (v) e a derivative which alkylates thiol-containing compounds to give a thioether-containing product.
30. (Currently amended) The kit of ~~claims 26 to 29~~claim 26, where the precursor is bound to a solid phase.
31. (Currently amended) Use of the imaging agent of ~~claims 1 to 15~~Claim 1 in a method of diagnosis of a caspase-3 implicated disease state of the mammalian body, wherein said mammal is previously administered with the pharmaceutical composition which comprises the imaging agent of Claim 1 together with a biocompatible carrier, in a form suitable for mammalian administration ~~of claim 16,~~



or the radiopharmaceutical composition which comprises the imaging agent of Claim 1 wherein the imaging moiety is radioactive, together with a biocompatible carrier, in a form suitable for mammalian administration ~~of claims 17 to 19.~~